



Complex Generic Drugs

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The views presented are those of the authors and do not necessarily reflect official views of the Food and Drug Administration.

GPhA Fall Technical Meeting

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Goals for Today

- How to get scientific questions about complex drugs into the regulatory science research program
- An update on our recent guidance on complex drugs
- How to submit a useful and successful pre-ANDA meeting requests for complex drugs

What are Complex Generic Drugs?

- Complex Active Ingredients
 - LMWH, peptides, complex mixtures, natural source products
- Complex Formulations
 - Liposomes, iron colloids
- Complex Route of Delivery
 - Locally acting drugs
- Complex Drug-Device Combinations
 - DPI, MDI, nasal spray, transdermal system

Complex Drugs ...

- Can have Generics (ANDA Approvals)
 - Enoxaparin (2011)
 - Sodium Ferric Gluconate (2011)
 - Doxorubicin HCl liposome injection (2013)
 - Acyclovir topical ointment (2013)
- Can be controversial
 - Citizen petitions on all of these
 - International differences (clinical studies for EMA)
 - Efforts to define non-biological complex drugs as a new category outside ANDA pathway
- Are more complex than other ANDA
 - More complex development
 - Longer reviews that impact GDUFA goals
 - One of the reasons for GDUFA support of regulatory science

GDUFA REGULATORY SCIENCE

GDUFA

FY 2013 Regulatory Science Accomplishments

- New External Collaborations
 - 20 Grants, 9 Contracts for \$17 million in Regulatory Science
- New Internal Collaborations
 - FDA lab (new equipment for Generic Drug Research: \$1 million)
 - 25 new ORISE fellows for Generic Drug Research (10 to FDA lab)
- New Guidance for Industry
 - First MDI BE guidance (April), First Ophthalmic Emulsion BE guidance (June), First DPI BE guidance (Sept)
- New Plan for FY 2014 Regulatory Science
 - Public Meeting and comments there and to the docket

June 2013 Public Meeting

- Slides, Transcripts, Video Available
 - <http://www.fda.gov/Drugs/NewsEvents/ucm344710.htm>
- Meeting Question on Complex Generics
 - Areas where additional draft guidance is needed to clarify FDA recommendations on complex generic drug product development
- Areas Identified
 - Statistical methodologies for in vitro equivalence and adhesion/irritation
 - Variability of dissolution for locally acting GI drugs
 - Acceptability of ANDAs for synthetic peptides

2013 Docket Comments: Summary

- QbD use cases for **complex products** (3 comments).
- Development of advanced in vitro dissolution methods, incorporating physiological factors and release models for **complex products** (2 comments).
- General and individual BE guidance for **complex dosage forms** (3 comments).
- BE standard for NTI drugs (2 comments).
- Post marketing surveillance (2 comments).
- Anti-epileptic drugs (3 comments).

GDUFA

FY 2014 Regulatory Science Priorities

<http://www.fda.gov/Drugs/NewsEvents/ucm367997.htm>

- Post-market Evaluation of Generic Drugs
- Equivalence of Complex Products
- Equivalence of Locally Acting Products
- Therapeutic Equivalence Evaluation and Standards
- Computational and Analytical Tools

FY 2014 Public Meeting on GDUFA Regulatory Science

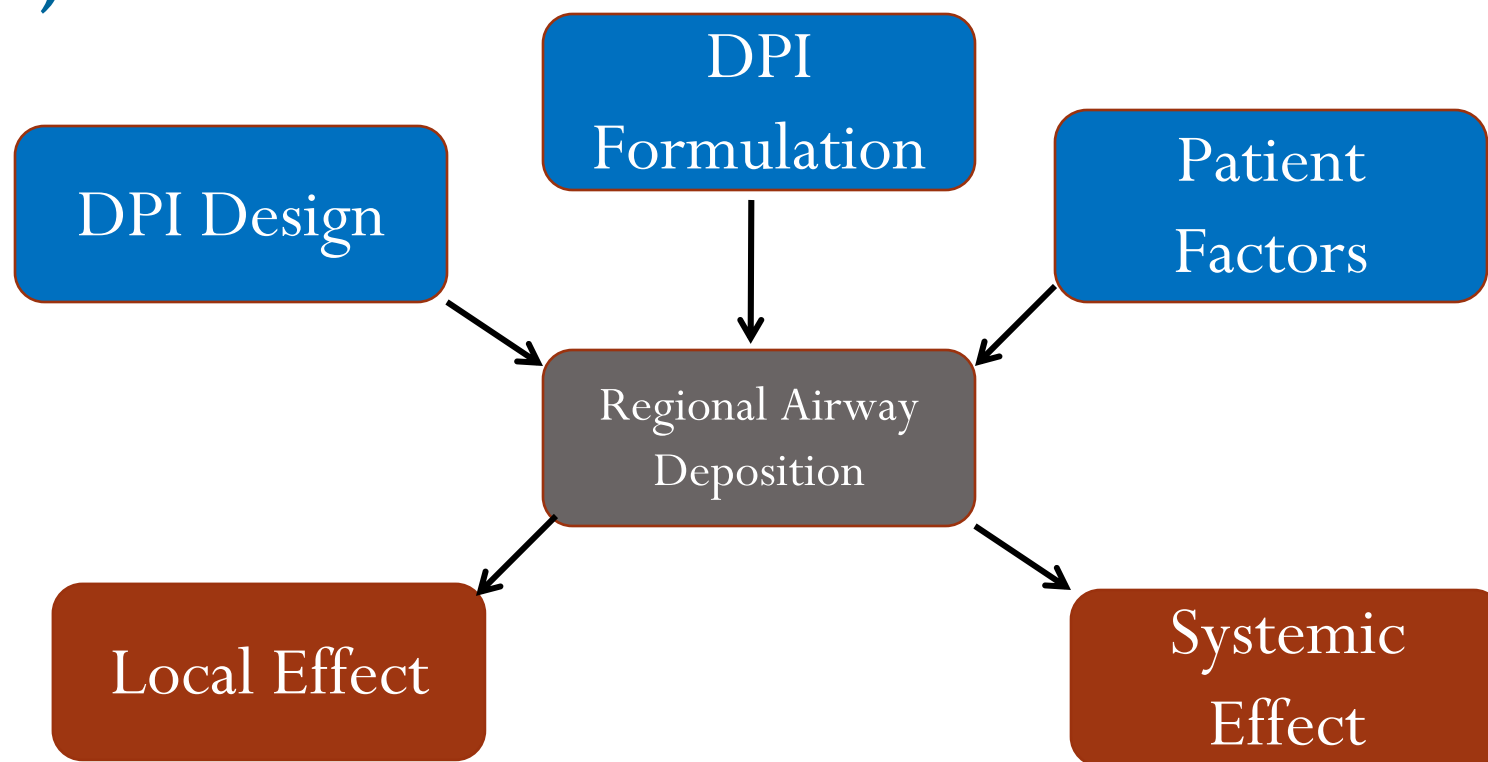
- GDUFA Regulatory Science Page
 - Source for updates
 - <http://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm370952.htm>
- FY 2014 Meeting
 - Q3 of FY 2014 at White Oak
 - Docket will be open
 - We would value more input from the generic industry

RECENT GUIDANCE

Bioequivalence of Metered Dose Inhalers (MDI)

- The first individual product guidance for a MDI has posted (Albuterol Sulfate April 2013)
 - <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM346985.pdf>
- Recommends in vitro, PK and PD equivalence studies
- Acceptance Limits on Dose Scale Confidence Intervals: 67-150%
 - Extensive simulation
 - For dose-scale analysis power for BE is driven by both within and between subject variability
 - For standard ABE we have methods for reference scaling on the within subject variability
 - These limits provide equivalent assurance of similarity as ABE limits of 80-125%

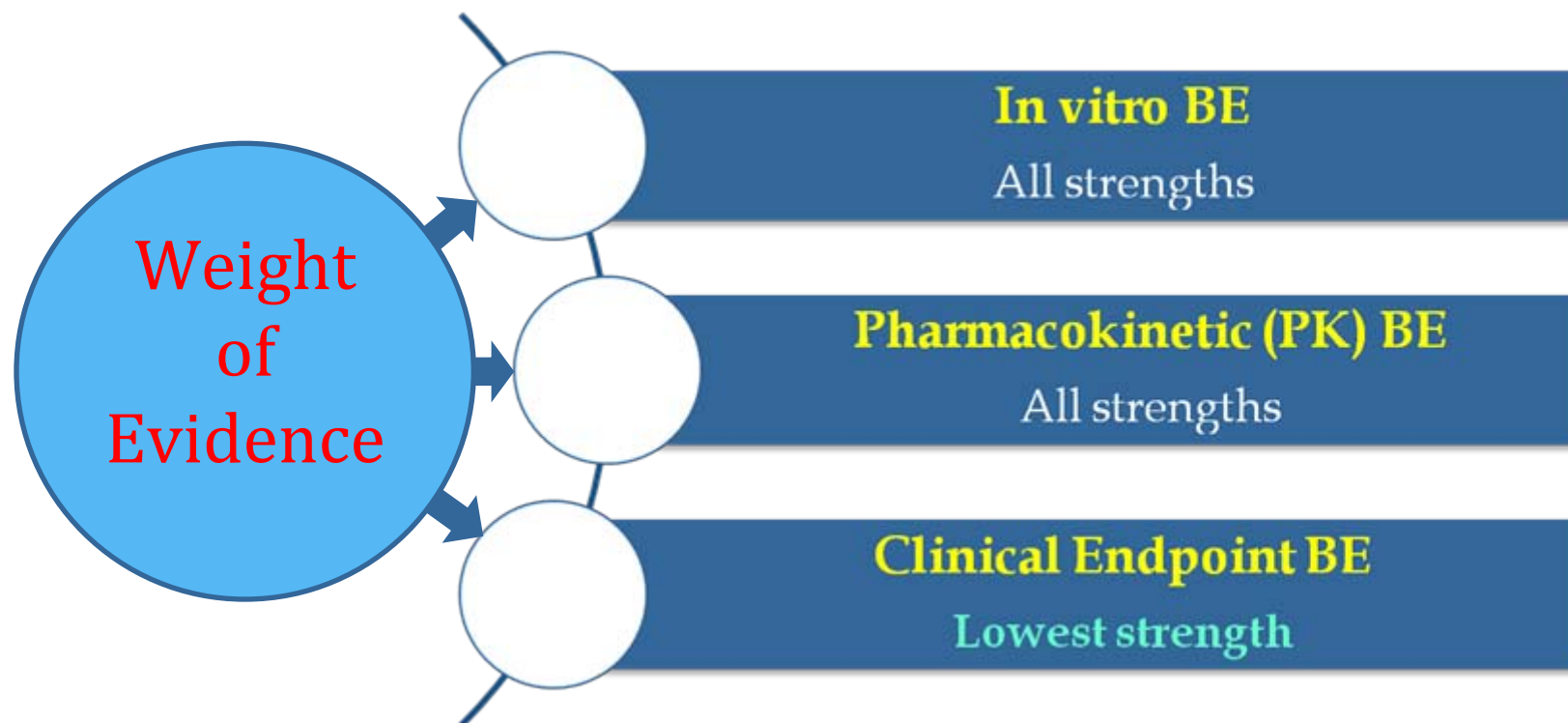
Bioequivalence of Dry Powder Inhaler (DPI)



First drug specific BE recommendation for DPI: Draft BE guidance for Fluticasone Propionate; Salmeterol Xinafoate (FP/SX) inhalation powder aerosol, published in September, 2013

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM367643.pdf>

BE Evaluation for Generic FP/SX DPI



Generic FP/SX DPI Device Recommendations

- Energy Source: Passive (breath actuated)
- Metering: Pre metered multi-dose format
- Number of Doses: 60
- External operating procedures: (1) Open, (2) Click, (3) Inhale, and (4) Close
- Similar size and shape to the RLD product
- Comparable device resistance to the RLD product
- Dose counter
- OGD recommends generic firms to send their working prototype for evaluation of device similarity



Bioequivalence of Local Acting Orally Inhaled Drug Products

New GDUFA Funded Research in FY 2013

- Development of in vivo predictive dissolution method for orally inhaled drug products
-<http://grants.nih.gov/grants/guide/rfa-files/RFA-FD-13-014.html>
- Systematic evaluation of excipient effects on the efficacy of metered dose inhaler products
-<http://grants.nih.gov/grants/guide/rfa-files/RFA-FD-13-013.html>
- Investigate the sensitivity of pharmacokinetics in detecting differences in physicochemical properties of the active in suspension nasal products for local action
-FY2013 Solicitation Number: FDA-SOL-1120918
- Pharmacokinetics of locally acting orally inhaled drug products

Other Guidance on Equivalence of Complex Drugs

- Doxorubicin Liposome

- <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM199635.pdf>

- Lidocaine Patch

- <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm086293.pdf>

- Mesalamine (multiple forms)

- <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM320004.pdf>

- Acyclovir Topical Ointment

- <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM296733.pdf>

- Cyclosporine Ophthalmic Emulsion

- <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358114.pdf>

MEETING REQUESTS

Meeting Process:

pre-ANDA Meeting on Complex Drugs

- Pre-ANDA Meetings are not covered by GDUFA
- Send pre-ANDA meeting request to OGD through
 - GenericDrugs@FDA.HHS.gov
 - Science Staff Scientific Coordinator: Kris Andre
- Evaluation
 - After assignment to a reviewer
 - Can we answer question via Control Correspondence process?
 - Request for more information, if necessary
- Response and Scheduling
 - Notification of meeting granted or denied
 - If meeting is denied, a Control Correspondence response to specific questions will be provided
- Meeting Preparation
 - Requester must provide final meeting package at least 4 weeks before scheduled meeting date
 - Internal pre-meeting held
 - Comments to requester a few days before
- Meeting Day
 - Some question may be answered in writing
 - Adjust agenda to focus on challenging questions
 - Use time wisely

Meeting Requests for Complex Drugs

- Pre-ANDA discussions were not part of OGD culture/process and are not part of GDUFA
- We want to grant more as resources increase
- pre-ANDA meetings help us meet the GDUFA ANDA goals by resolving complex issues before submission, improve submission quality, and reduce review cycles
- But we cannot grant them all

– FY 2013 Statistics

Meeting Requests to OGD Science	Held or Scheduled	Denied or Withdrawn	Pending
21	5	6	10

What is in a Successful Meeting Request

- Impact
 - A product with no generics available
 - A product with unique regulatory science issues
- Clarity of Purpose
 - Clear and specific questions proposed
 - An proposed agenda must be included
- New Data
 - Data that is new to OGD
 - Pilot studies of an alternative approach

What is in an Unsuccessful Meeting Request

- Fishing for approaches
- Problems without proposed solutions
- Questions that can be answered in controlled correspondence
- Non-specific agenda
- Scope too broad
- No specific questions (get acquainted request)
- No data

Shared Vision of Regulatory Science Success for Complex Drugs

- Both FDA and Generic Industry Have a Common Customer
 - Patients who want high quality generic products in all product categories
- Pre-ANDA Discussion Can Advance Regulatory Science
- Pre-ANDA Discussion Should Lead to Better ANDA Submissions

Thanks! OGD Science Staff

- Thushi Amini (Research Coordinator)
 - GDUFA Regulatory Science Implementation
 - Grants and Contracts
- Kris Andre (Scientific Coordinator)
 - External Meetings
 - Workflow Management
 - Control Correspondence
- Staff: Wenlei Jiang, Yih-Chain Huang, Bavna Saluja, Stephanie Kim, Susie Zhang, Pradeep Sathe, Jeff Jiang
- Fellows: Nan Zheng, Renish Delvadia, Bryan Newman, Andrew Babiskin, Lei He, Denise Conti, Poonam Delvadia, Wendy Cai, Yan Wang, Kunyi Wu, Wen Qu, Priyanka Ghosh, Weixuan He